Depression is a state of low mood and aversion to activity that affects person's thoughts, behavior, feelings and physical well-being. Depressed people feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, or problems concentrating, remembering details or making decisions; and may contemplate or attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains or digestive problems that are resistant to treatment may be present (Zimmerman, 2004). Depressed mood is not necessarily a psychiatric disorder. Depressed mood is a normal reaction to certain life events, a symptom of some medical conditions, and side-effect of some medical treatments. Depressed mood is also a main or common feature of certain psychiatric syndromes such as clinical depression (Mc-Pherson and Martin, 2010).

Depressed mood can be the result of a number of infectious diseases and physiological problems including Addison's disease, Lyme disease, multiple sclerosis, sleep apnea and disturbed circadian rhythm. It is often one of the early symptoms of hypothyroidism (reduced activity of the thyroid gland). A number of psychiatric syndromes feature depressed mood as a main symptom. The mood disorders are a group of disorders considered to be primary disturbances of mood. These include major depressive disorder (MDD), commonly called major depression or clinical depression, where a person has at least two weeks of depressed mood or a loss of interest or pleasure in nearly all activities; and dysthymia, a state of chronic depressed mood, the symptoms of which do not meet the severity of a major depressive episode. Another mood disorder, bipolar disorder, features one or more episodes of abnormally elevated energy levels, cognition and mood, but may also involve one or more depressive episodes. Outside the mood disorders, borderline personality disorder
commonly features depressed mood, and adjustment disorder with depressed mood is a mood disturbance appearing as a psychological response to an identifiable event or stressor, in which the resulting emotional or behavioral symptoms are significant but do not meet the criteria for a major depressive episode (APA, 2000).

**PREVALENCE**

Centers for Disease Control and Prevention analysis of Behavioral Risk Factor Surveillance System survey data from 2006 and 2008 found nine percent of 2,35,067 adults surveyed in 45 states, District of Columbia, Puerto Rico, and US Virgin Islands 3.4% met the criteria for current depression (defined as meeting criteria for either major depression or "other depression" during the 2 weeks preceding the survey). By state, age-standardized estimates for current depression ranged from 4.8% in North Dakota to 14.8% in Mississippi according to Centre for disease control and Prevention, 2010.

**ETIOLOGY**

The specific cause of major depressive disorder is not known. As with most psychiatric disorders, major depressive disorder appears to be multifactorial in its origin. According to the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters for depressive disorders in childhood and adolescence, a history of a previous depressive episode, subsyndromal symptoms of depression, dysthymia, and anxiety disorders increase the risk for future depression. Symptoms of major depression in adolescence strongly predicted adult episodes of major depression in a study of an epidemiologic sample of 776 adolescents by Pine and associates (Pine et al., 1999).
Genetics

Genetic susceptibility plays a role in the development of major depressive disorder. Individuals with a family history of affective disorders (7%), panic disorder, and alcohol dependence (8%) carry a higher risk for major depressive disorder. Studies such as those reported by Akiskal and Weller, (1989) and Weissman et al., (1984) suggest a genetic component in the etiology of depressive disorders. Nobile et al., (1999) found that human platelet 5-HT (5-hydroxy tryptamine) uptake is differentially influenced in children with and without depression by a common genetic variant of the promoter region of 5-HT. Birmaher et al., (1997) found that, before onset of affective illness, children who were at high risk had the same pattern of neuroendocrine response to 5-hydroxy-L-tryptophan (L-5-HTP) challenge as did children with major depression. These findings could constitute the identification of a trait marker for depression in children.

Some evidence suggests that late-onset depression (after age 60 years) is an etiologically and clinically distinct syndrome (Blazer, 2003) and that genetic factors play less of a role in late-onset than early-onset depression. A family history of depression is less common among older adults with depression than younger adults. However, certain genetic markers have been, although inconsistently, associated with late-onset depression, including polymorphisms of the apolipoprotein E, brain derived neutropic factor (BDNF), and 5-hydroxy tryptamine transporter genes. Interestingly, these markers have also been associated with cognitive impairment, hippocampal volume, and antidepressant response, respectively.
Stressors

Although major depressive disorder can arise without any precipitating stressors, stress and interpersonal losses certainly increase risk. Psychodynamic formulations found that significant losses in early life predispose to major depressive disorder over the lifespan of the individual, as does trauma, either transient or chronic. Depression is a behavioral response to repeated stressors and cognitive distortions (ie, negative thoughts) contribute to and perpetuate depressed mood. Chronic pain, medical illness, and psychosocial stress also play a role in both the initiation and maintenance of major depressive disorder. Older adults may perceive medical illness as psychologically distressing, and these illnesses may lead to increased disability, decreased independence, and disruption of social networks (Bruce, 2002). Other psychosocial risk factors for depression in late life include the following (Ohara et al., 1984):

- Impaired social supports
- Caregiver burden
- Loneliness
- Bereavement
- Negative life events

In addition, neurochemical hypotheses point to the deleterious effects of cortisol and other stress-related substances on the neuronal substrate of mood in the central nervous system (CNS). Exposure to certain pharmacologic agents also increases the risk of depression; medications such as reserpine or beta-blockers, as well as abused substances such as cocaine, amphetamine, narcotics, and alcohol, are associated with higher rates of major depressive disorder. A meta-analysis that
including all relevant studies exploring the interaction between a serotonin transporter promoter polymorphism (5-HTTLPR) and stress in the development of depression suggested that 5-HTTLPR moderates the relationship between stress and depression (Karg et al., 2011).

**Neuroendocrine abnormalities and neurodegenerative diseases**

Prepubertal children who were depressed had lower cortisol secretion during the first 4 hours of sleep than did children in the control group, according to De-Bellis et al., (1996) who studied neuroendocrine changes in depressed prepubertal children. The investigators examined nocturnal secretion of adrenocorticotropin (ACTH), cortisol, growth hormone (GH), and prolactin (PL) in the groups with depression and control groups, ACTH, GH, and PL secretion did not differ between the two groups.

**Possible abnormalities of the neurotransmitter systems remain under investigation**

Neurodegenerative diseases (especially Alzheimer disease and Parkinson disease, stroke, multiple sclerosis, seizure disorders, cancer, macular degeneration, and chronic pain have been associated with higher rates of depression (Krishnan, 2002).

**Parent-child relations**

The parent-child relation model conceptualizes depression as the result of poor parent-child interaction. Adults with depression report low paternal involvement and high maternal overprotection during early childhood. Troubled relationships with parents, siblings, and peers are common in children and adolescents with affective illness. A child who is affectively ill often has a parent who is affectively ill. It is not uncommon for children to report abuse and/or neglect by parents who are affectively
ill. Childhood abuse and neglect, as well as a cumulative load of stressors over a lifetime, have both been associated with late-onset depression. Hammen et al., (1991) reported a significant temporal association between mother and child. They found that children with substantial stress exposure who also had symptomatic mothers were significantly more depressed than children who were exposed to comparable levels of stress only.

**Vascular depression**

The vascular depression hypothesis posits that cerebrovascular disease may cause or contribute to late-life depression. Various lines of evidence support this hypothesis, including the following (Thomas et al., 2004):

- Higher incidence of depression following a stroke
- Higher prevalence of ischemic white-matter changes in older adults with depression than those without
- Bidirectional association between depression and coronary artery disease (CAD)
- Higher rates of depression among patients with vascular dementia than those with Alzheimer disease

**EPIDEMIOLOGY**

The lifetime incidence of major depressive disorder in the United States is 20% in women and 12% in men. The prevalence is as high as 10% in patients observed in a medical setting. Klerman (1988) and Gershon et al., (1987) reported a progressive increase in the lifetime cases of major depression over the last 70 years, with high rates of affective disorders among relatives and a younger age of onset in successive cohorts. In 2010, the Center for Disease Control and Prevention (CDCP)
released a report estimating the prevalence of current depression among adults during 2006-2008. Among 2,35,067 adults, 9% met the criteria for current depression, including 3.4% who met the criteria for major depression. Internationally reported adult prevalence rates of depression generally mirror those of the United States, and estimates of prevalence of depression among community-dwelling elderly are surprisingly consistent (eg, England, 2.9%; The Netherlands, 2.0%; Sweden, 5.6%; Nigeria, 1.6%). However, sparse data are available on the international incidence of major depression in children and adolescents.

Helgason examined the entire Icelandic birth cohort of 1895-97 with periodic follow-up until cohort individuals reached age 74-76 years. The lifetime estimates of risk for any affective disorder were 14.8% for females and 9.8% for males (Helgason, 1964). The World Health Organization (WHO) collaborative study on the assessment of depressive disorders found considerable similarity in depressive symptomatology across cultures in Canada, Iran, Japan, and Switzerland (Jablensky et al., 1981). The Stirling County Study, which began shortly after World War II, offered a 40-year perspective of the prevalence and incidence of psychiatric disorders among an adult population in Atlantic Canada, in which the overall prevalence of depression remained stable at 5% across 3 separate samples in 1952, 1970, and 1992. In the year 2000 sample, however, the prevalence had shifted from older to younger persons, and the female-to-male ratio had increased (Murphy et al., 2000).

Copeland et al., (1999) found widely ranging prevalence’s for depression in elderly persons in 9 European populations. The prevalence for females was higher than that for males, and there was no constant association between prevalence and
age. Meta-analysis revealed an overall prevalence of 12.3% and sex frequencies of 14.1% for females and 8.6% for males.

**Children and adolescents**

In prepubertal children, boys and girls were affected equally. Hankin et al., (1998) found that the most critical time for sex differences in depression is from age 15-18 years. During this period, the increase of the overall rates of depression and onset of new cases of depression peak. The incidence of depression was 0.9% in preschool-aged children, 1.9% in school-aged children, and 4.7% in adolescents in a study by Kashani and Sherman, (1988). More than 22% of female high school students and more than 11% of male high school students reported 1 current or lifetime episode of unipolar depression in one study. In the same study, the percentage of male students with 2 or more episodes of unipolar depression was 4.9%; it was 1.6% in female students (Lewinsohn et al., 1993).

Hispanic youths in Los Angeles country (aged 12-17 years) reported more symptoms of depression, independent of socioeconomic status, when compared with white, black, or Asian American adolescents, according to an epidemiologic study by Siegel et al., (1998). This study also found significant effects of social class on depression. As income decreased, the average level of depression increased. The 1-year incidence of major depression was 3.3% in adolescents aged 11-16 years in the southeastern United States (Garrison et al., 1997).

**Elderly persons**

Although rates of depression in women and men are highest in those aged 25-44 years, the incidence of clinically significant depressive symptoms increases with advancing age, especially when associated with medical illness or institutionalization.
However, the depression might not meet criteria for major depression because of somewhat atypical features of depression in elderly persons.

**Minor depression and major depression**

The prevalence of minor depression or subsyndromal depression is likely higher than that of major depressive disorder; levels of functional impairment, medical burden, and quality of life are lower than in major depressive disorder but higher than in older adults without any depression (Arean and Cook, 2002).

**PROGNOSIS**

Major depressive disorder is a disorder with significant potential morbidity and mortality, contributing as it does to suicide, medical illness, disruption in interpersonal relationships, substance abuse, and lost work time. With appropriate treatment, 70-80% of individuals with major depressive disorder achieve a significant reduction in symptoms, although as many as 50% of patients may not respond to the initial treatment trial. Forty percent of individuals with major depressive disorder untreated at 1 year will continue to meet criteria for the diagnosis, whereas an additional 20% will have a partial remission. Pretreatment of irritability and psychotic like symptoms are associated with poorer outcomes. Partial remission and/or a history of chronic major depressive disorders are risk factors for recurrent episodes and treatment resistance.

**Late-onset depression**

The prognosis of late-onset depression is felt to be poorer in the elderly than in younger patients, and it appears to be dependent on physical handicap or illness and lack of social support. Of particular importance is the increasing risk of death by suicide, particularly among elderly men. In older patients, depression is frequently
comorbid with chronic medical conditions and can lead to worsening medical outcomes, including mortality; patients with depression have higher usage of medical services. For example, coronary artery disease is a risk factor for the development of depression, and depression is an independent risk factor for the development of coronary disease. Patients with both conditions are more likely to die than those with coronary artery disease alone. Both behavioral and physiological explanations are likely for these associations (Lesperance and Smith, 2007).

Millard suggested the "rule of thirds" concerning the prognosis of late-onset depression, which states that regardless of treatment, approximately one third of patients will manifest remission, another one third will remain symptomatic in the same condition, and the remaining one third will worsen (Millard, 1983). In fact, research has shown that approximately 60% of patients with late-onset depression will have at least 1 recurrence, and up to 40% of these patients will have chronic or continuously recurrent depression (Alexopoulos and Choster, 1992). Late-onset depression has been reported to double the risk of developing mild cognitive impairment (Geda et al., 2006) and the likelihood that the mild cognitive impairment will develop into dementia (Modrego and Ferrandez, 2004). Compared with participants without depression history, those with late-life depression reportedly have increased all-cause dementia risk; however, early life depression had no association with dementia risk (Li et al., 2011). Treating depression has been suggested to possibly stunt progression to mild cognitive impairment and from there to dementia, although there has been little evaluation of this hypothesis to date.
Suicide

Depression plays a role in more than one half of all suicide attempts, whereas the death rate from suicide among those with affective disorders exceeds 15%. According to Centers for Disease Control and Prevention (CDC) data, suicide was the eleventh leading cause of death in the United States in 2006, accounting for 33,300 deaths, and it continues to rank as the second leading cause of death in adolescents and the third leading cause of death in people aged 15-24 years. However, despite these data and the fact that depression is more often diagnosed in women, the highest suicide rate is in men older than 75 years; more men than women die from suicide by a factor of 4.5:1. White men complete more than 78% of all suicides, and 56% of suicide deaths in males involve firearms. Poisoning is the predominant method among females. In addition to older age and male sex, risk factors for suicide include the following (Conwell et al., 2002; Elovainio et al., 2009):

- Diagnosis of major depression
- Previous history of suicide attempt
- Burden of medical disease and presence of current serious medical condition (although this risk may be mediated by a diagnosis of depression)
- Recent stressful life events, especially family discard
- Lack of social support
- Being widowed or divorced
- The presence of a gun in the home
- Unexplained weight loss

The use of antidepressants may in fact be a protective factor (Friedman and Leon, 2007).
Studies also show that major depressive disorder contribute to higher mortality and morbidity in the context of other medical illnesses, such as myocardial infarction, and that successful treatment of the depressive episode improves medical and surgical outcomes. Suicide rates among American Indian and Alaskan natives between ages 15 and 34 years are almost twice the national average for this age range. Hispanic females make significantly more suicide attempts than their male or non-Hispanic counterparts. In 2005, 1.4% of all deaths worldwide were attributed to suicide. The real number is unknown, as underreporting is predictably significant. Suicide is estimated to be the eighth leading cause of death in all age ranges. In Eastern Europe, 10 countries report more than 27 suicides per 1,00,000 persons. Latin America and Muslim countries report the lowest rates, with fewer than 6.5 cases per 1,00,000.

PATHOPHYSIOLOGY OF DEPRESSION

The underlying pathophysiology of major depressive disorder has not been clearly defined. Clinical and preclinical trials suggest a disturbance in central nervous system (CNS) serotonin (5-HT) activity as an important factor. Other neurotransmitters implicated include norepinephrine (NE) and dopamine (DA) (Dunlop and Nemeroff, 2007).

The role of CNS 5-HT activity in the pathophysiology of major depressive disorder is suggested by the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depressive disorder. Furthermore, studies have shown that an acute, transient relapse of depressive symptoms can be produced in research subjects in remission using tryptophan depletion, which causes a temporary reduction in CNS 5-HT levels. Serotonergic neurons implicated in affective disorders are found in the dorsal raphe nucleus, the limbic system, and the left prefrontal cortex. Seasonal
affective disorder is a form of major depressive disorder that arises during the winter and resolves during the spring and summer. Studies suggest that seasonal affective disorder is also mediated by alterations in CNS levels of 5-HT and appears to be triggered by alterations in circadian rhythm and sunlight exposure.

Vascular lesions contribute to depression by disrupting the neural networks involved in emotion regulation in particular, fronto striatal pathways that link dorso lateral prefrontal cortex, orbito frontal cortex, anterior cingulate, and dorsal cingulate cortex (Alexopoulos, 2005). Other components of limbic circuitry, in particular the hippocampus and amygdala, have been implicated in depression. Functional neuro imaging studies support the hypothesis that the depressed state is associated with decreased metabolic activity in neocortical structures and increased metabolic activity in limbic structures (Mayberg et al., 1999). In recent years, an abnormality in an area of the brain that helps to control emotional reactions has been found and contributes to a new understanding of why persons develop depression and other affective disturbances. By using positron emission tomographic (PET) images, researchers found an area of the prefrontal cortex with an abnormally diminished activity in patients with unipolar depression and bipolar depression. This region is related to emotional response and has widespread connections with other areas of the brain. These other areas are responsible for the regulation of DA, Noradrenaline (NA), and 5-HT, which have important roles in the regulation of mood.

An integrative model of late-onset depression states that age-related brain changes and disease-related changes (eg, cerebrovascular disease), coupled with physiologic vulnerabilities (eg, genetic risk factors, personal history of depression) and psychosocial adversity, lead to disruptions in the functional circuitry of emotion.
regulation (namely, hypometabolism of cortical structures and hypermetabolism of limbic structures), resulting in the clinical manifestations of depression (Alexopoulos, 2005). Endocrine changes in depression are evident across the life span, but some are unique to aging. Women with a previous history of depression are at higher risk of developing depression during menopause, suggesting a role for estrogen in mood regulation; low testosterone levels have been associated with depression in older men.

**Neurotransmitters and Mood**

Neurotransmitters, especially noradrenaline, serotonin and dopamine are believed to be key in the control of mood and emotional behavior.

1. Noradrenaline and the Noradrenergic System

The noradrenaline system is referred to as the noradrenergic system, and receptors specific to noradrenaline or adrenaline are both referred to as adrenergic receptors. Noradrenaline, which is synthesized from the dietary amino acid tyrosine, is believed to play a major role in the control of mood and emotional behavior. The major concentration of noradrenergic neurons is in the locus ceruleus in the midbrain. The axons of these neurons project upward through the forebrain to the cerebral cortex, the limbic system, the thalamus, and the hippocampus. Noradrenaline, a key neurotransmitter involved in the control of mood and emotional behavior, is believed to inhibit or stimulate a variety of emotional responses such as anxiety, aggression, stress, and sleep patterns. Noradrenaline is released by a presynapse, and binds to receptor sites on a postsynaptic neuron. Residual noradrenaline (NE) is taken back up into the presynaptic neuron (reuptake) where it is recycled into storage vesicles or metabolized by the enzyme monoamine oxidase (MAO degradation).
2. Serotonin and the Serotonergic System

Like noradrenaline, serotonin (5-HT) is a key neurotransmitter involved in the control of mood. The axons of serotonergic neurons originate in the raphe nuclei of the brain stem and project to the cerebral cortex, the limbic system, cerebellum, and spinal cord. Serotonin is involved in the regulation of pain, pleasure, anxiety, panic, arousal, and sleep behavior (the sleep-wake cycle). Serotonin (5-HT) is synthesized from a dietary amino acid called tryptophan. Like noradrenaline, serotonin is a neurotransmitter. As such, serotonin is released by a presynaptic neuron, travels across a synapse, and binds to a receptor site in a postsynaptic neuron.

3. Neurotransmitter Receptor Sites

There are different types of neurotransmitters, there are different receptor sites, each with an affinity for a specific neurotransmitter. In addition to the receptor sites located on postsynaptic neurons in the brain, receptor sites exist on neurons in other parts of the body, such as the gut or salivary glands. (The side effect profile of antidepressant drugs varies with their affinity for these receptors). In recent years, many subtypes of these receptors have been discovered. Some adrenergic receptors, are now known to be associated with inhibitory processes while others are stimulatory. While the science of mood disorders is still very incompletely understood, some very useful theories have emerged over the past two decades.

Theories of Depression

✓ The Biogenic Amine Hypothesis
✓ The Receptor Sensitivity Hypothesis
✓ The Serotonin-only Hypothesis
The Biogenic Amine Hypothesis.

In the early 1950s, researchers noticed that drugs that decreased monoamines precipitated depression, and drugs that increased monoamines relieved depression. The Biogenic Amine Hypothesis states that depression is caused by a deficiency of monoamines, particularly noradrenaline and serotonin. According to this hypothesis, depression can be alleviated by drugs that increase the availability of noradrenaline and serotonin. One method of increasing monoamines centers around the action of monoamine oxidase (MAO). Blocking the action of MAO leads to an increased availability of neurotransmitters. When the action of MAO is blocked, neurotransmitters are not metabolised, so they accumulate in the presynaptic neuron. Drugs which block the metabolism of noradrenaline and serotonin via inhibition of MAO are called MAO inhibitors (MAOIs). MAOIs were among the first clinically proven antidepressants. Taken chronically, MAOIs also produce desensitization and down-regulation of postsynaptic receptors. Another way to increase monoamines involve blocking the process of reuptake. Blocking reuptake prevents the presynaptic neuron from reclaiming neurotransmitter, which increases the amount of neurotransmitter in the synaptic cleft.

Drugs were developed in the 1950s that blocked reuptake in just this way. These drugs - still widely used today - are called tricyclic antidepressants or TCAs. The Biogenic Amine Hypothesis has been the cornerstone of research on depression for more than 30 years. However, an important fact cannot be explained by the
Biogenic Amine Hypothesis. TCAs and MAOIs increase available neurotransmitters quite rapidly within a matter of hours. Yet, typically, clinical relief takes much longer. A person suffering from depression may not experience significant relief for as long as 6 to 8 weeks.

**The Receptor Sensitivity Hypothesis**

The Biogenic Amine Hypothesis alone cannot explain the delay in time of onset of clinical relief of depression of up to 6-8 weeks. Supersensitivity is a compensatory response of the postsynaptic neuron when it receives too little stimulation. The neuron tries to make up for a lack of stimulation by increasing receptor responsiveness. Over time, the postsynaptic neuron also compensates for lack of stimulation by synthesizing additional receptor sites. This process is known as up-regulation. By increasing the amount of neurotransmitter in the cleft, response is normalized. Increased neurotransmitter increases stimulation of receptor sites, which prompts the postsynaptic neuron to compensate by decreasing receptor sensitivity, a process known as desensitization. The postsynaptic neuron is also thought to compensate for increasing stimulation by decreasing the number of receptor sites, a process known as down-regulation.

Antidepressant drugs are thought to work by increasing the amount of neurotransmitters in the cleft. They do this by blocking metabolism of monoamines the MAOIs or by blocking reuptake the TCAs. Most TCAs are more effective in blocking noradrenaline reuptake than serotonin reuptake. Chronic administration of TCAs or MAOIs is thought to alter the responsiveness and/or the number of postsynaptic receptor sites. Observation of this long-term effect of antidepressants led to the Receptor Sensitivity Hypothesis.
This hypothesis proposes that depression is the result of a pathological alteration (supersensitivity and up-regulation) in receptor sites, which results from too little stimulation by monoamines, i.e., a deficiency of noradrenaline and serotonin in the cleft. Chronic administration of TCAs or MAOIs results in increased availability of noradrenaline and serotonin. This causes desensitization (the uncoupling of receptor sites) and possibly down-regulation (a decrease in the number of receptor sites). According to this hypothesis, relief from depression symptoms comes from a normalization of receptor sensitivity.

According to the Receptor Sensitivity Hypothesis, antidepressant drugs achieve their clinical effect by reducing receptor supersensitivity. This theory is an important step toward understanding the long delay between administration of TCAs and MAOIs and clinical response. While TCAs are effective in blocking the reuptake of noradrenaline and serotonin into the presynaptic neuron, they are non-selective: they also block postsynaptic receptor sites, including cholinergic (muscarinic), histaminergic, and adrenergic receptor sites. Blockade of histaminergic receptors lead to sedation, weight gain, and hypotension. In the elderly, this is a particular problem, since it results in fainting or falls. TCAs also block muscarinic receptors, which lead to blurred vision, dry mouth, constipation, urinary retention, confusion, and delirium.

**The Serotonin-only Hypothesis**

Early in the 1980s, drugs were introduced that selectively blocked serotonin reuptake, resulting in more serotonin available in the cleft. These drugs were known as selective serotonin reuptake inhibitors, or SSRIs. Unlike the TCAs, which are non-selective, the SSRIs have fewer serious side effects and are therefore easier for
patients to tolerate. This has led to the Serotonin-only Hypothesis which emphasizes the role of serotonin in depression and downplays noradrenaline.

But the serotonin-only theory has shortcomings:

1. It does not explain why there is a delay in onset of clinical relief;

2. It does not explain the role of noradrenaline in depression.

A study at Yale tested the serotonin-only hypothesis and demonstrated the importance of noradrenaline. The test group consisted of depressed patients who were being treated successfully with either selective serotonin reuptake inhibitors (SSRIs) or a non-selective TCA. All these patients were placed on a tryptophan-free diet. Researchers reasoned that serotonin alone was responsible for depression, only those patients taking SSRIs relapsed, while those on TCAs did not. This suggested that both noradrenaline and serotonin play a critical role in depression. When noradrenergic neurons are destroyed in laboratory animals, drugs that affect serotonin do not have their usual effects. Likewise, when serotonergic neurons are destroyed, drugs that affect noradrenaline do not have their usual effects.

The Permissive Hypothesis

Mood is controlled by a balance of noradrenaline and serotonin, not by absolute levels of these neurotransmitters or their receptors. According to this hypothesis - the Permissive Hypothesis - the control of emotional behavior results from a balance between noradrenaline and serotonin. According to this theory, both the manic phase and the depressive phase of bipolar disorder are characterized by low central serotonin function. Evidence suggests that brain serotonin systems dampen or inhibit a range of functions involving other neurotransmitters. Mood disorders result from the removal of the serotonin damper. The Permissive Hypothesis postulates that
low levels of serotonin permit abnormal levels of noradrenaline to cause depression or mania. If serotonin cannot control noradrenaline, and noradrenaline falls to abnormally low levels, the patient becomes depressed. On the other hand, if the level of serotonin falls and the level of noradrenaline becomes abnormally high, the patient becomes manic. According to this hypothesis, antidepressant drugs are effective to the degree that they reinstate the ability of serotonin to control noradrenaline, thus restoring the critical balance that controls emotional behavior.

A new class of antidepressant drugs, serotonin-noradrenaline reuptake inhibitors (SNRIs) work to selectively block reuptake of both noradrenaline and serotonin, thereby increasing levels of both monoamines. The SNRIs have very little affinity for other postsynaptic receptor sites and are therefore less likely to produce some of the side effects associated with TCAs.

The Electrolyte Membrane Hypothesis

This hypothesis largely died out after the 1960s but may be reemerging with the resurgence in the literature in the biochemistry and biophysics of membrane functions. For example, the lithium-sodium counter flow mechanism in red cells has been described and protein structural differences between patients with bipolar-polar disorder and controls have been revealed. The mechanism of action of lithium in bipolar disorder is still not understood.

The Neuroendocrine Hypothesis

According to this hypothesis, pathological mood states are explained or contributed to by altered endocrine function. This theory historically grew out of observations that altered mood states were associated with thyroid or Cushings disease. Current explorations of pathophysiology using neuroendocrine theories have
tended to result in research tools such as the dexamethasone suppression test becoming diagnostic tools, perhaps prematurely.

Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis.

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression (Neumeister et al., 2002; 2004a), possibly mediated by increased brain metabolism in the ventromedial prefrontal cortex and subcortical brain regions. Experimentally reduced central serotonin has been associated with mood congruent memory bias, altered reward-related behaviors, and disruption of inhibitory affective
processing (Hasler et al., 2004), all of which add to the clinical plausibility of the serotonin deficiency hypothesis.

There is also evidence for abnormalities of serotonin receptors in depression, with the most solid evidence pointing to the serotonin-1A receptor, which regulates serotonin function. Decreased availability of this receptor has been found in multiple brain areas of patients with Major Depressive Disorder (MDD) (Drevets et al., 1999), although this abnormality is not highly specific for MDD and has been found in patients with panic disorder (Neumeister et al., 2004b) and temporal lobe epilepsy (Hasler et al., 2007), possibly contributing to the considerable comorbidity among these conditions. However, there is no explanation for the mechanism of serotonin loss in depressed patients, and studies of serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem research on the serotonergic system in depression, have yielded inconsistent results. There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, cause serotonin deficiency (Meyer et al., 2006). In addition, loss of functional mutations in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 explain the loss of serotonin production as a rare risk factor for depression (Zhang et al., 2005).

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of MDD, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients. In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1 adrenergic receptor density have been found in the brains of depressed suicide victims post-mortem (Pandey and
Dwivedi, 2007). Since there is no method to selectively deplete central norepinephrine and no imaging tool to study the central norepinephrine system, solid evidence for abnormalities of this system in depression is lacking.

While the classical theories of the neurobiology of depression mainly focused on serotonin and norepinephrine, there is increasing interest in the role of dopamine (Nutt, 2006). Dopamine reuptake inhibitors (e.g., nomifensine) and dopamine receptor agonists (e.g., pramipexole) had antidepressant effects in placebo-controlled studies of MDD (Goldberg et al., 2004). In the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover (Lambert et al., 2000). Striatal dopamine transporter binding and dopamine uptake were increased in MDD, consistent with a reduction in dopamine neurotransmission (Meyer et al., 2001). Degeneration of dopamine projections to the striatum in Parkinson’s disease was associated with a major depressive syndrome in about one half of cases, which usually preceded the appearance of motor signs (Santamaria et al., 1986).

Experimentally reduced dopaminergic transmission into the accumbens has been associated with anhedonic symptoms and performance deficits on a reward processing task in subjects at increased risk of depression (Hasler et al., 2008; Hasler et al., 2009). These findings are consistent with the clinical observation that depressed patients have a blunted reaction to positive reinforcers and an abnormal response to negative feedback (Murphy et al., 2003). Almost all established antidepressants target the monoamine systems (Mann, 2005). However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Despite this limitation, the monoamine deficiency
hypothesis has proved to be the most clinically relevant neurobiological theory of depression. New findings on the role of dopamine in depression emphasize the scientific potential of this theory, and promising reports of antidepressant effects of drugs that modulate the dopaminergic system (e.g., pramipexole, modafinil) in difficult-to-treat depression underline its clinical relevance (Fava et al., 2005). The development of neuroimaging techniques has opened up the potential to investigate structural and functional abnormalities in living depressed patients.

**FACTORS INFLUENCING DEPRESSION**

**Biogenetic risk factors**

Twin, adoption and family studies are the genetic factors influenced the genetic vulnerability factors of depressive disorder (Hamet and Tremblay, 2005). Genetic variation causes biological dysregulation associated with depression. It was observed that the functional polymorphism in the promoter region of the serotonin transporter gene moderates the influence of stressful life events on depression (Capsi et al., 2003). Its temperamental characteristics are harm avoidance and reward dependence associated with specific biological function increase the vulnerability to depression (Cloninger et al., 1993; Heath et al., 1994).

**Psychological factors**

Cognitive phenomena such as schemas and automatic thoughts mediate depression emotion and behavior (Golagman et al., 1998; Young et al., 2003).

Stressful events can activate these dysfunctional schemas, facilitate cognitive distortions and result in automatic thoughts which reflect the negative triad about the self, world and future (Beck et al., 1979).
Apart from genetic aspects, intergenerational factors also increase the vulnerability to depression. Impaired social skills, excessive interpersonal dependency and excess interpersonal inhibition are three other non-exclusive domains of vulnerability to depression (Joiner et al., 2002).

**Somatic risk factors**

Physical illness such as pain, thyroid disease, immunity problem, cancer, viral infections, cardio vascular system (CVS) and skin disorders increase the vulnerability to depression. Drug abuse, intoxication with or withdrawal from substances such as alcohol, amphetamine and sedatives increased the vulnerability to depression.

**Social–cultural risk factors**

Socio-cultural activities such as nuclear family, extra familial structures or traditional social cultures break down leads to less intergenerational continuity and which causes less importance to family values results in depression. American paradox, economic expansion and increased social recession such as high number of divorcee, suicide, violence leads to depression (Myer, 2000).

**Environmental factors**

Depression has both genetic and environmental factors. Chronic mild stress (CMS) is a key factor in the environmental component of depression. Exposure to CMS causes depression. Chronic mild stress causes atrophy of CA3 pyramidal neurons of hippocampus include a decrease in the number and length of apical dendrites (Duman et al., 1997) and decrease proliferation of cells in the dentate gyrus of the hippocampus along with the alteration in processes and number of neurons (Gould et al., 2002). CMS altered AMPA–receptor glu-R1 sub unit level in hippocampi and nucleus accumbens exerts different neurobiochemical and
behavioural resilience. Volumetric and cellular loss occurs in the subgenual frontal cortex in depressive patients as a result of down regulation of brain derived neurotropic factor (BDNF) levels in hippocampus attributing to atrophy of neurons and reduced neurogenesis in the hippocampus and subgenual frontal cortex. BDNF and Glu- system plays a role in the neuronal plasticity which may be involved in the pathophysiology and treatment of mood disorder (Zangen and Shavlev, 2003).

TREATMENT

Antidepressants hold the third rank among the most prescribed of therapeutic agents’ world wide. There are about two dozen antidepressants agents which function by nine different pharmacological distinct functions (Stahl, 1998). Antidepressants act indirectly by enhancing 5HT tone or 5HT receptors through the inhibition of reuptake and presynaptic 5HT_{1A} autoreceptors are a primary target of several antidepressants which enhance the extracellular 5HT or act directly (Haddad et al., 1998; Blier and Ward, 2003).

The conventional antidepressants act by producing effective changes in the corticosteroid receptors of HPA axis followed by clinical recovery (Holsber, 2000) and prevents atrophy either by blocking or opposing the stress induced death (Manji et al, 2000; Gould et al., 2002).

Mechanism of action of Antidepressants

Neurotransmitter action is terminated by the uptake by transporters which are present both on neurons and astrocytes (Fullers and Wong, 1990; Bal et al., 1997; Inaz et al., 2001). Elevation of norephrine (NE) levels by the blockade of uptake has a profound effect on astrocytic neurotransmitter receptor expression and cellular signalization cascade modulation. Astrocytes express beta1 and beta 2
adrenoreceptors in the brain (Hostli and Hosli, 1993) responds to antidepressants by decreasing the density of receptors (Sapena et al., 1996). The following are the possible mechanism of action

- TCAs prevent presynaptic reuptake of the amines (NA and 5HT)
- MAOIs reduce the activity of MAO in breaking down presynaptic amines (leaving more available for release into the presynaptic cleft.
- Some may block post synaptic receptors directly (Brown and Bennet, 2003).
- Mainly inhibits the reuptake of biogenic amines 5HT, norepinephrine and dopamine into presynaptic nerve terminals.
- Enhances uptake of monoamines on the synapses and reversed the stress induced changes in hippocampal formation and modulate glutamate receptor function.
- TCAs regulate tyrosine hydroxylase activity in dopaminergic brain regions including cell body and terminal field of mesolimbic and nigrostriatal pathways of the rat brain (Rosine et al., 1995).
- SSRIIs acts by inhibiting serotonin transport and it increases serotonin in somatodendritic area of serotonergic neurons.
- Monoamine oxidase inhibitors shows immediate action but its clinical response requires weeks or months.
- Down regulation of monoamines occurs directly from postsynaptic action and betadrenergic 5HT receptors at postsynaptic level and shows proximal effects on G-receptor coupled to G protein and distal effects of G protein to
effector enzymes with added effect on adenylacyalse and phosphsholipase
(Avissar and Scheriber, 2006).

The initial delay in clinical action results from neurobiological adaptive
mechanism secondary to the activation of primary target which encompasses changes
in presynaptic activity of monoamine containing neurons and Postsynaptic effect
in corticolimbic area.

CHRONIC ADMINISTRATION OF ANTIDEPRESSANTS

Enhances uptake of monoamines on the synapses and is supposed to reverse
the stress induced changes in the hippocampus formation and modulate glutamate
receptor function (Mc-Even et al., 2002).

✓ Significantly increases the glial derived neurotropic factor (GDNF) release
from C6 glioma cells which is further potentiated by HT (Hisoka et al., 2001).

✓ Norepineprine stimulates C6 glioma and cortical astrocytic cells to produce
glial derived neurotropic factor via beta adrenergic receptor stimulation and
adenylcylase activation (Arisan et al., 1989). Decreased monoamine receptor
densities in cell culture system such as C6 glioma cell lacking presynaptic
cleft.

Activation of beta adrenoreceptors induces the synthesis of nerve growth
factor, fibroblast growth factor (FGF), transforming growth factor (B1, B2) hence
provide neuroprotection against glutamate induced and ischemic neuronal damage
(Junker et al., 2002).

✓ Prolonged administration causes desensitization of some 5HT1A receptors,
which in turn no longer inhibit neuronal impulse flow hence, turned on
(Richelson, 1982). This reaction causes increased release of 5HT from axon terminals leading to desensitization of postsynaptic 5-HT receptors at final step. This desensitization result in therapeutic action of SSRIs. The desired pharmacological profile of SSRI is to produce powerful and delayed disinhibition of 5HT neurotransmission in the pathway from mid brain raphe to prefrontal cortex is presumed to mediate the antidepressant effect of SSRI (Baxter et al., 1989; Foote and Morrison, 1987; Blier and De-Monotny.,1994).

All monoamines increase BDNF astrocyte synthesis, secretion suggests the existence of positive reciprocal interaction between monoaminergic neuronal activity and astrocyte cross talk which has a dynamic role in mediating neuronal plasticity and tropic functions in the brain (Mojcaurie et al., 2006).

Up regulation of BDNF into mid brain denotes antidepressant effect. BDNF is known to influence the survival and function of mature neurons and characterized by their action during development and maturation of neurons.

Down regulation of post synaptic beta adrenergic receptors, 5HT₁ and 5HT₂ receptors at post synaptic level, in response to chronic administration.

ANIMAL MODELS OF DEPRESSION

Earlier studies revealed that structural alterations occur in response to stress in rats, but are reversible upon administration of antidepressants (Manji et al., 2000). Swimming is one of the most common analytical technique used to surrender or resistance to fatigue or depression (Zhang et al., 2002, Nestler et al., 2002b).
Different animal models of depression are:

- **Learned helplessness (LH)**

  The LH paradigm uses a stress-exposure period in which rats or mice are exposed to inescapable stress (e.g., electrical foot shock) in one or more sessions. In a subsequent session, the animals are tested for their performance in an active avoidance test. In a typical active avoidance test, animals are confined to one side of a shuttle box chamber where foot shocks are delivered but the animal has the opportunity of actively escaping the foot shock. Animals previously exposed to inescapable stress show reduced abilities to escape in this model. The reduced ability to escape is restored by different forms of antidepressant treatment, including tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive shock therapy (Martín et al., 1990; Sherman et al., 1982). This model has good validity for predicting antidepressant efficacy (Willner, 1984).

- **Forced swim test (FST)**

  The FST involves placing a rat or mouse in a cylinder with enough water so that it cannot touch the bottom with its hind paws (Porsolt et al., 1977a,b, 1978). A normal animal will show an immediate burst of activity, try to escape, and then eventually adopt an ‘‘immobile’’ posture, where it will make only those movements necessary to keep its head above water. The development of immobility may be facilitated by prior exposure to the test and a 24-h prior preexposure to the test is often used (Porsolt et al., 1978). Immobility is quantified during brief test periods and classical antidepressants such as the monoamine oxidase inhibitors, tricyclics, and atypical antidepressants all decrease the duration of immobility in rats and mice in a dose-dependent manner (Borsini and Meli, 1988; Porsolt et al., 1977a,b).
- **Tail suspension test (TST)**

  The TST is conceptually similar to the FST and is suggested to have greater sensitivity. A mouse is suspended by the tail in this test and observed for the extent of immobility versus active movement (Steru et al., 1985). Similar to the FST, the TST is also based on the adoption of a passive response in a stress situation. Acute antidepressant treatment given prior to the test reduces immobility time in the TST and it is considered to have good predictive validity (Cryan et al., 2005; Perrault et al., 1992; Steru et al., 1985).

- **Hyponeophagia paradigms**

  Examples of hyponeophagia tests that are used in rats and mice are novelty induced hypophagia (NIH) and novelty suppressed feeding (NSF) paradigms. They are anxiety based and compare feeding behavior in an anxiogenic versus a nonanxiogenic environment. The stress employed in these models is very mild relative to most other tests for antidepressant action, and consists of placing the experimental animal in a novel environment to induce anxiety during testing. The animal experiences conflict between the desire to approach and feed or drink, and the anxiety-induced avoidance of the novel environment (Dulawa et al., 2004).

- **Chronic unpredictable mild stress**

  In comparison to LH and FST/TST procedures that rely on relatively short term aversive stress exposure, the chronic unpredictable mild stress (CUS) paradigm was developed to study neural changes that result from stress of a more chronic nature. CUS paradigms aim to model a chronic depressive like state that develops gradually over time in response to stress, and is thus considered more naturalistic in the induction. Rats or mice are exposed to a series of different stress conditions over a
period of several weeks. Several stressors (6–8) are applied (1 or 2 per day) for several hours each day. Typical stressors include overnight illumination, periods of food or water restriction, cage tilt, and isolation or crowded housing. The sequential and unpredictable stress exposure decreases the likelihood of the animals habituating to any one reoccurring condition (Aguilera, 1998; Magarin˜os and McEwen, 1995; Tannenbaum et al., 2002).

- **Hedonic sensitivity**

  Methods for quantifying hedonic sensitivity include conditioned place preference procedures in which animals learn to associate a particular environment with reward experience, brain stimulation reward (BSR) paradigms, and quantifying consumption of sweet solutions. Quantifying consumption of sweetened fluids (sucrose or saccharin) is the most commonly employed endpoint for assessing CUS effectiveness. Rats previously habituated to sucrose are typically given a choice of drinking sucrose versus water in a two-bottle test. While control rats typically show a preference for drinking weak sucrose solutions, rats exposed to CUS loose this preference. The development of this effect can be demonstrated by repeated sucrose preference testing during the course of CUS exposure. The time-dependent reversal of this effect with chronic antidepressant treatment can also be demonstrated by repeated testing.

- **Early life stress (ELS)**

  Early life adverse experience is an important predisposing factor for psychopathology in humans. Several human studies indicate that exposure to stress or adversity early in life increases the risk for depression, and that stress exposure may interact with genetic risk factors (Agid et al., 1999, 2000; Caspi et al., 2003; Kaufman
et al., 2006; Weiss et al., 1999). The ELS models typically employ stress exposure during critical periods of development and result in stable phenotypic changes. ELS-induced changes that have been particularly replicable involve alterations in neural systems that regulate or respond to stress such as the hypothalamus pituitary axis and include endocrine, neurochemical, and behavioral alterations.

- **Social defeat**

  Social stress represents a significant type of adversity in many species and is thought to play a role in the development of depression and other psychopathology in humans (Agid et al., 2000; Bjorkqvist, 2001; Huhman, 2006).

  The use of social conflict as a stressor and the use of social interaction as a quantifiable endpoint both have validity for depression (Heim and Nemeroff, 2001). Experimental models in rodents frequently utilize a conflict situation that results in one animal becoming or retaining dominant status and another ending up subordinate or “defeated”. A phenotypic trait produced in these models is social avoidance, which can be quantified and is suggested to model social withdrawal in human depression (Berton et al., 2006; Koolhaas et al., 1997; Van-Kampen et al., 2002).

**LIMITATIONS**

Depressive patients are unwilling to take medication as the depression affects both physical and mental conditions. Less than 20% of the affected receive medication, and less than 10% take suitable medication, though the inhibitory action of antidepressants on reuptake of monoamine are immediate, but their clinical response requires weeks of treatment (Lepine et al., 1997; Parikah et al., 1999; Hyman, 1999). Among the antidepressants SSRIs constitutes 80% of antidepressants, response rate of SSRIs is about 60 % at 6 weeks whereas clinical response is
estimated as 50 % decrease in initial severity. Other antidepressants such as SNRI or TCAs inhibit the reuptake of noradrenaline, the presence of side effects limits its use. The effects of clinical therapies are not desirable. Cessation of medication is common in clinical treatment (Anderson and Tomenson, 1995; Pampallona et al., 2002). Patients are unwilling to continue medication due to severe side effects leading to poor compliance and poor therapeutic effect (Demyttenare, 2003).

ADVERSE EFFECTS OF CONVENTIONAL ANTIDEPRESSANTS

Tricyclic antidepressants

TCAs inhibit sodium channels at high dose leads to cardiac arrhythmia, seizures, anxiety, sleep disturbances, sexual dysfunction and gastrointestinal disturbances (Richelson, 1982).

Selective serotonin reuptake inhibitors

SSRIs cause anxiety, akathisia, insomnia and sexual dysfunction, decreases appetite, nausea, weight loss (Stahl, 1998; Balon, 1997; Stein and Hollander, 1994).

Noradrenaline specific reuptake inhibitors

NRIs cause dryness of mouth, constipation, sexual dysfunction (DeBattista and Shatzberg, 2000).

Monoamine oxidase inhibitors

MAOIs produce weight gain, CNS stimulation, liver damage and convulsions. Lithium salts causes diarrhoea, thyroid enlargement, hypothyroidism, tremor and renal effects.
Noradrenaline and dopamine reuptake inhibitors

Noradrenaline and dopamine causes psychomotor retardation, anhedonia, hypersomnia, cognitive slowing, craving inattention, pseudodementia (Breese et al., 1974).

TRADITIONAL MEDICINE

World Health Organization (WHO) offers the collective term Traditional medicine (TM) to refer systems of medicine such as traditional Chinese, Indian Ayurveda, Arabic Unani and various systems of indigenous medicine. TM is also referred as Complementary or Alternative or Non Conventional Medicine (WHO, 2002).

ADVANTAGES OF TRADITIONAL MEDICINE (TM)

✓ Easy availability, accessibility, affordability though quality and mechanism differ in various parts of the World.

✓ Many of the developing countries are on the increased consumption due to limited availability and accessibility of Modern medicine which is expensive and often unaffordable.

✓ Available at the local level and easily affordable (Zhang, 2004).

✓ Adds the advantage that it has no drug interventions.

✓ It has right quality of material and apt processes are used from sourcing to marketing.

✓ No contamination, adulteration or spiking (Kaened, 1999).
Emerging diseases where no medicines are available have provoked the interest in medicinal plants as a significant source of new medicine (Dhaunkar et al., 2000).

Cost effective and has limited systematic studies to compare.

Contain several chemicals substances, its medicinal action are due to the co-operation of the constituents.

Possess natural affinity to the body system, non specific, normalizing action shows minimal disturbances in cellular environment, minimal psychological changes.

Recent studies supported the general belief of TM as affordable over modern medicine (Ernest, 2000; Evans, 1997).

Systematic Pharmacognostical, detailed Phytochemical investigations and innovative Pharmacological studies provide scientific information on the quality, efficacy, safety or toxicity of traditional drugs of plant origin which will enhance the standardization and acceptance of Traditional medicine globally.

**Table 1 List of medicinal plants reported to possess antidepressant effect**

<table>
<thead>
<tr>
<th>Biological name</th>
<th>Parts used</th>
<th>Family</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Argyreia nervosa</em></td>
<td>Root, leaf</td>
<td>Convolvulaceae</td>
<td>Chopra et al., 1956</td>
</tr>
<tr>
<td><em>Baccopea moniera</em></td>
<td>Whole plant</td>
<td>Scrophulariceae</td>
<td>Aithal and Sirsi, 1961</td>
</tr>
<tr>
<td><em>Banux Houpei</em></td>
<td>Whole plant</td>
<td>Chinese formulation</td>
<td>Luol et al., 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wang et al., 2005</td>
</tr>
<tr>
<td><em>Casimiroa edulis</em></td>
<td>leaf</td>
<td>Rutaceae</td>
<td>Mora et al., 2005</td>
</tr>
<tr>
<td><em>Celastrus paniculatus</em></td>
<td>Seeds and oil</td>
<td>Celestraceae</td>
<td>Nalini et al., 1995</td>
</tr>
<tr>
<td><strong>Centella asiatica</strong></td>
<td>Whole plant</td>
<td>Umbelliferae</td>
<td>Ganachari et al., 2004</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Cimifuga racemosa</strong></td>
<td>leaf</td>
<td>Ranunculaceae</td>
<td>Borrelli and Ernst, 2003; Winterhoff, 2000</td>
</tr>
<tr>
<td><strong>Clitoria ternata</strong></td>
<td>Whole plant</td>
<td>Leguminosae</td>
<td>Norte et al., 2005; Cosentino and Mc-Norte, 2004</td>
</tr>
<tr>
<td><strong>Crocus sativus</strong></td>
<td>stigma</td>
<td>Iridae</td>
<td>Akhonda et al., 2005</td>
</tr>
<tr>
<td><strong>Croton zehnterni</strong></td>
<td>leaves</td>
<td>Euphorbiaceae</td>
<td>Guorgi et al., 1991</td>
</tr>
<tr>
<td><strong>Elaeocarpus senticosus</strong></td>
<td>Seed fruit</td>
<td>Tiliaceae</td>
<td>Singh et al., 2000</td>
</tr>
<tr>
<td><strong>Gastrodia elata</strong></td>
<td>leaves</td>
<td>Orchidaceae</td>
<td>Zhou et al., 2006</td>
</tr>
<tr>
<td><strong>Glycyrrhiza glabra</strong></td>
<td>Root, rhizomes</td>
<td>Leguminosae</td>
<td>Dinesh and Sharma, 2005</td>
</tr>
<tr>
<td><strong>Ginkgo biloba</strong></td>
<td>Root</td>
<td>Gingoboeacea</td>
<td>Sakakaribari et al., 2006</td>
</tr>
<tr>
<td><strong>Hibiscus subdariffa</strong></td>
<td>Leaves</td>
<td>Malvaceae</td>
<td>Amos et al., 2003</td>
</tr>
<tr>
<td><strong>Hypericum perforatum</strong></td>
<td>Aerial parts</td>
<td>Hypericeae</td>
<td>Sanchez et al., 2002; Butterweck et al., 1984</td>
</tr>
<tr>
<td><strong>Panax ginseng</strong></td>
<td>Root</td>
<td>Arilaceae</td>
<td>Atlele et al., 1999; Rudakawich et al., 2001</td>
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<tr>
<td><strong>Passiflora foetida/alata</strong></td>
<td>leaves</td>
<td>Passilforacea</td>
<td>Flavino, 2001</td>
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<tr>
<td><strong>Polygala tenurifolia</strong></td>
<td>Root</td>
<td>Polygalaceae</td>
<td>Ikaya and Tunkava, 2004</td>
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<td><strong>Salvia elegans</strong></td>
<td>Leaves</td>
<td>Labitae</td>
<td>Maribel et al., 2006</td>
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<td><strong>Securda longepedunculata</strong></td>
<td>Leaves</td>
<td>Polygalaceae</td>
<td>Adebiye et al., 2006</td>
</tr>
<tr>
<td><strong>Withania somniferum</strong></td>
<td>Root</td>
<td>Solaneceae</td>
<td>Bhattacharya et al., 2009</td>
</tr>
</tbody>
</table>
**ARGYREIA NERVOSA (AN)**

<table>
<thead>
<tr>
<th>Botanical Source</th>
<th>Argyreia nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td></td>
</tr>
<tr>
<td><strong>Family</strong></td>
<td>Convolvulaceae</td>
</tr>
<tr>
<td><strong>Synonym</strong></td>
<td>Argyreia speciosa</td>
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**VERNACULAR NAMES**

<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
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<tbody>
<tr>
<td>English</td>
<td>Elephant creeper</td>
</tr>
<tr>
<td>Telugu</td>
<td>Samudrapalai</td>
</tr>
<tr>
<td>Tamil</td>
<td>Samudrapaccha</td>
</tr>
</tbody>
</table>

**CLASSIFICATION**

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subkingdom</td>
<td>Tracheobionta  (Vascular plants)</td>
</tr>
<tr>
<td>Superdivision</td>
<td>Spermatophyta (Seed plants)</td>
</tr>
<tr>
<td>Division</td>
<td>Magnoliophyta  (Flowering plants)</td>
</tr>
<tr>
<td>Class</td>
<td>Magnoliopsida  (Dicotyledons)</td>
</tr>
<tr>
<td>Subclass</td>
<td>Asteridae</td>
</tr>
<tr>
<td>Order</td>
<td>Solanales</td>
</tr>
<tr>
<td>Family</td>
<td>Convolvulaceae</td>
</tr>
<tr>
<td>Genus</td>
<td>Argyreia</td>
</tr>
<tr>
<td>Species</td>
<td>nervosa</td>
</tr>
</tbody>
</table>
Habitat

The plant grows on river banks, edges of lakes and as an under-growth in semi deciduous forests climbs over bushes to elevation of 1000 m found throughout India and often cultivated in Western regions (Nadkarni, 1994a).

Botanical description of the plant

AN is soft woolly climber with hardy woody stalk bearing soft silky heart shaped leaves of 9-12 cm long and 8-10 cm breadth. Leaves are larger with acute apex and cordate base. Flowers are purple, silky pubescent and wooly inside with bract. Corolla is rosy and wooly. Calyx is white, tomentose outside with glabrous ovary inside. Fruits are globose and indehiscent berry (Nadkarni, 1994a; Varier, 1997a).

Ethnoclaims

In India, the leaves are used to prevent conception by the tribals of Rajasthan, whereas in Assam and Bihar leaves are used as vegetable (Wealth of India). Roots are used as an appetizer, anti-inflammatory, aphrodisiac, expectorant, cardiotonic and brain- tonic. Roots are used to treat obesity, diabetes, anemia, ulcers, wounds, synovitis and gonohorrea (Varier, 1997a). Leaves are used to treat boils, swellings, ring worm infestations, externally to treat itches, eczema, wounds and skin diseases (Asima and Satyesh, 2003a). In Hindu medicine, the root is used as alternative tonic and used for rheumatic affections and diseases of the nervous system (Nadkarni, 1994a).
**Phytochemical Review**

**Seeds**

Miller, (1970) isolated and identified lysergic acid (LSD), isolysergic acid and ergoline alkaloids from the seeds of *Argyreia nervosa*. They were identified by thin layer chromatography, melting point, ultraviolet and infrared spectroscopical methods.

Chaos and Mardersian, (1973) reported the presence of nineteen indole alkaloids in the seeds of *Argyreia* and were identified by thin layer chromatography and paper chromatography.

In particular lysergene, festuculine, setoclavine, iso-clavine, agroclavine, elmyoclavine, ergine and isoergine were isolated by column chromatography and was characterized by thin layer chromatography and infra red analysis. Penniclavine, chanoclavine - I and II, ergometrine, ergometrinine, lysergic acid (LSD), alpha hydroxyl ethylamide, isolysergol, racemic chanoclavine–II, molliclavine, lysergol and iso-lysergic acid, α-hydroxyl iso-lysergic acid were identified by thin layer chromatography. Ergine and isoergine were found in high concentration. Lysergine, setuclavine, iso-setoclavine, chanoclavine–II, iso-setoclavine, iso-lysergol and molloclavine were identified for the first time in the species.

Agarwal and Rastogi, (1974) identified the presence of ergometrine, other related constituents such as caffeic acid and ethyl caffeate in AN.

Mann et al., (1999) reported the presence of N-formylloline alkaloids and flavanoidal sulphates from the roots of AN. Shukla et al., (1999) isolated hydroxy-cinnmate and scopeltin from the roots of AN.
Rahman et al., (2003) isolated argyroside from the seeds of AN, a steroidal glycoside chemically named as 24 R ergost-5-en-11-oxe-3beta–ol–alpha D-glucopyranoside whose structure was elucidated by spectroscopic analysis and chemical methods.

**Pharmacological Review**

**Antimicrobial activity**

Mishra and Chaturvedi, (1978) reported the antibacterial and antifungal effect for the oil isolated from the seed of AN.

**Antifungal and phytotoxic activity**

Shukla et al., (1999) isolated hydroxycinnamate and scopeltin from AN and were screened against fungi. AN showed significant antifungal effect against *Fusarium fusiformis*, *Fusarium semitectum* and *Alternaria alternate* and exhibited complete inhibition of root growth in germinated wheat.

**Anti-inflammatory activity**

Gokhlae et al., (2002) administered ethanolic extracts of AN at the dose of 50, 100, 200 mg/kg orally and studied anti-inflammatory activity in acute and chronic rat inflammatory models. AN showed significant anti-inflammation effect by reduction in paw edema and prevented the accumulation of inflammatory cells.

**Immunomodulatory effect**

Gokhale et al., (2003) administered aqueous extract of AN at the dose of 50, 100, 200 mg/kg to sheep red blood cells and oxazolone induced hypersensitive mice. AN showed significant immunomodulatory effect by increased production of
antibodies and white blood corpuscles (WBC) cells in mice and restored the myleosuppressive effects induced by cyclophosphamide.

**Antidiarrhoeal activity**

Hydroalcoholic extract of flowers of AN was administered at the dose of 50, 100 and 150 mg/kg orally and showed significant antidiarrhoeal effect by inhibition of intestinal propulsion and reduction in faecal matters (Rao et al., 2004).

**Aphrodisiac property**

Subramoniam et al., (2007) reported enhancement of mating and mounting behaviour in mice with aqueous extract of roots, leaves and flowers of AN.

**Nootropic effect**

Joshi et al., (2007) reported nootropic activity of aqueous extract of roots of AN in scopolamine and diazepam induced memory impairment in passive avoidance paradigm and elevated plus maze and was attributed to inhibition of acetylcholine esterase activity.

**Analgesic and anti-inflammatory**

Alcoholic and aqueous extract of AN of root was administered at the dose of 30, 100, 300 mg/kg to inflammatory models of mice. AN showed significant analgesic effect by increased basal reaction time in hot plate, inhibited the writhing induced by acetic acid and reduced the paw edema (Bacchav et al., 2009).
**Effect on central nervous system**

Hydroalcoholic extract of AN was administered at the dose of 100, 200 and 500 mg/kg to rats was subjected to neuropharmacological screening. AN showed significant dose dependent reduction in spontaneous motor activity and potentiated pentobarbital sodium induced sleep (Galani and Patel, 2009).

**Anticonvulsant activity**

Vyawahare and Bodhankar, (2009) studied the effect of hydroalcoholic extract of various doses of AN root were administered to pentylenetetrazole and maximal electrical shock induced convulsions in rats. AN showed significant anticonvulsant effect against pentylenetetrazole and maximal electrical shock induced convulsions.

**Anti obesity effect**

Shivkumar et al., (2011) reported that ethanolic extract of roots of AN was administered to rats. AN showed significant antiobesity effect by decreased weight of liver and adipose tissue.
JASMINUM SAMBAC (JS)

Botanical Source  
Jasminum sambac
Leaves

Family  
Oleaceae

Synonym  
Arabian Jasmine

VERNACULAR NAMES

English  
Jasmine

Telugu  
Mallgae

Tamil  
Malli

CLASSIFICATION

Kingdom  
Plantae (Plants)

Subkingdom  
Tracheobionta (Vascular plants)

Superdivision  
Spermatophyta (Seed plants)

Division  
Magnoliophyta (Flowering plants)

Class  
Magnoliopsida - Dicotyledons

Subclass  
Asteridae

Order  
Scruphulariales

Family  
Oleaceae.

Genus  
Jasminum.

Species  
sambac
Habitat

It is grown as an ornamental shrub in gardens and cultivated throughout the tropical and subtropical parts of India (Dastur, 1952a).

Botanical description of the plant

JS is a sub erect shrub with young shoots of ovate or elliptic glabrous simple leaves, entire margin, acute apex and opposite arrangement. Flowers are white, solitary, and fragrant with lobed calyx. Fruits are globose, berries and blue black when ripen (Asima and Satyesh, 2003b; Varier, 1997b).

Ethnoclaims

In China flowers of JS are used to flavour the tea. Leaves, roots and flowers are used as lactifuge. The whole plant is used as diuretic, emmengogue, antihelminthtic and deobstruent. Otto from flowers is used as deodorant and balsam from leaf preparations are used to treat insanity (Nadkarni, 1994b).

Phytochemistry Review

Root

Zheng et al., (2004) reported the presence of dotricontanol, oleanolic acid, daucosterol and hesperidin and dotriacontanic acid from the roots of JS by spectral and physical methods.

Flowers

Inagaki et al., (1995) reported the presence of glycosidic precursors such as benzyl 6-O- β-D-xylo pyranosyl β-glucopyranoside (beta–primeveroside), 2- phenyl ethyl β primeveoroside, 2- Phenyl ethyl 6-O– alpha L–rhamnoside.

Ana et al., (2008) reported the presence of alkaloids, glycosides and tannins from the stem and leaves of JS.
Pharmacological Review

Anti-lactation activity

Shrivastav et al., (1988) reported that paste of flowers of JS applied to breast suppressed puerperal lactation. JS flowers showed significant antilactation effect by reduction in serum prolactin.

Antiviral effect

Chiang at al., (2003) reported that flowers of JS at the concentration of 100-150 microgram/ml exhibited significant antiviral effect against simplex and adenovirus.

Antibacterial activity


Antiproliferative activity

Wamidh and Mahanesh, (2010) reported significant anti-proliferative activity of flower extracts of JS against HEP-2 (breast epithelial adenocarcinoma), MCF-7(larynx carcinoma) and Vero African green monkey kidney cell lines.

Antimicrobial and antiacni activity

Tsung et al., (2010) reported antimicrobial and antiacne effect of JS against Propionibacterium acnes evaluated by the production of cytokines in human monocyte cells.
Anti inflammatory

Methanolic extract of JS showed the inhibitory effects on the proinflammatory mediator secretion in coculture of THP-1 cells with heat killed Propionibacterium acne (Tsung et al., 2010).
PASSIFLORA FOETIDA (PF)

Part used  
Passiflora foetida leaves

Family  
Passifloraceae.

Synonyms  
Passion flower

VERANACULAR NAMES

English name  
Passionflower, Stinking Passion.

Telugu  
Tellajumuki.

Tamil  
Siruppunnaikali.

CLASSIFICATION

Kingdom  
Plantae

Division  
Magnoliophyta

Class  
Magnolipsida

Order  
Malpighiales

Family  
Passifloraceae.

Genus  
Passiflora

Species  
foetida.
Habitat

It is common plant grown in South India found at an elevation of 500 m, throughout moist and damp places (Nadkarni, 1994c).

Botanical description of the plant

PF is a perennial tendril climber with hispid, thin wiry woody stem, covered with sticky yellow hairs. Leaves are 5-10 cm long, equally wide, trilobed, viscid, hairy, acute apex, sub cordate base; hispid-hirsute on both sides holding a petiole 2-5 cm. Flowers are solitary in axils, 4-5 cm wide, purple and white with 3-7.5 cm long pedicled. Fruits are sub-globose, yellowish orange to red when ripe, thin leathery skinned 2 -3 cm thick with numerous seeds (Nadkarni, 1994c).

Ethnoclaims

PF is used by Gond tribes for cancer (Tiwari and Padhye, 1993), decoction of the leaves are used for giddiness and headache (Karnick, 1994), asthma (Nadkarni, 1994c; Vedavathi et al., 1997b), in Suriname traditional practice it is used to treat nervous disorders and as expectorant in Brazil. PF is also used as sedative and antihypertensive (Capasso and Sorrentino, 2005).

Phytochemical Review

Leaves and stem

Kapoor et al., (1972) reported the presence of alkaloids and flavanoids from the stems and leaves of PF. Lutomski and Malek, (1975) reported the presence of harmaline alkaloids in PF. Mabry et al., (1982) reported the presence of C-glycosides from the leaves of PF. Echverri et al., (2001) reported three polypeptides, alpha pyrones and passiflorines from the hydroalcoholic extract of aerial parts of PF.
Seeds

Siriamorupur and Yang, (2005) measured the total lipids by gravimetric method and its fatty acid composition was analyzed by gas liquid chromatography (GLC). The percentage of lipid content was found to be 19-47%.

Leaves

Pongapan et al., (2007) reported the amount of vitexin (0.04 to 0.13% w/w) by reverse phase (RP-HPLC) High performance liquid chromatography technique using an isocratic elution with mobile phase composing of isopropanol: tetrahydrofuran : water (5:15:80v/v) and 0.3 % formic acid. Bendini et al., (2007) reported the phenolic content of PF quantified by Spectrophotometric methods, HPLC and Mass Spectrometry.

Pharmacological Review

Insect deterrent activity

Echverri et al., (1991) reported ten flavones and glycosides isolated from leaf resin of PF. PF showed significant insect deterrent activity at the concentration of 40 ppm against Dione Juno larvae.

Leishmanicidal and cytotoxic activity

**Antiproliferative activity**

Ethanolic extract of PF showed antiproliferative effect against SKBR3 human breast adenocarcinoma cell lines using MTT assay (Pongapan et al., 2004).

**Hypoglycemic activity**

Alcoholic extract of leaves of PF was administered at the dose of 100 and 200 mg/kg body weight to alloxan-induced albino rats. PF showed significant reduction in blood glucose in alloxan treated rats (Dhanabal et al., 2004).

**Antibacterial activity**

Mohanasundari et al., (2007) reported antibacterial effect of ethanol and acetone extracts of leaf and fruits at the dose of 100, 200, 300 and 400mg/mg against the strain *Pseudomonas putida, Vibrio cholerae, Shigella flexneri* and *Streptococcus pyrogens*.

**Antimelanogenesis activity**

Ethanolic extract of fruit and stem of PF showed antimelanogenesis effect by 1,1 – diphenyl 2-picryl hydrazyl (DPPH) radical scavenging assay, tyrosinase inhibition activity and melanin formation inhibition assay using B16 melanoma cells. PF showed significant inhibition of melanin production in B16 melanoma cells cytotoxicity (Arung et al., 2009).

**Anti-oxidant activity**

Methanolic extracts of PF showed antimicrobial activity against *E. coli* which was tested by agar diffusion and turbidity assays. PF exhibited antioxidant effect against *E. coli* (Bendini et al., 2007).
SAPINDUS EMARGINATUS (SE)

Part used: *Sapindus emarginatus leaves*

Family: Sapindaceae.

Synonyms: *Sapindus laurifolio /
Sapindus trifoliatus*

**English:** Soapnut tree

**Hindi:** Ritha

**Telugu:** Kunkutikaya,

**CLASSIFICATION**

Kingdom: Plantae

Division: Phenerogamia

Class: Dicotyledon

Series: Disciflorae

Subclass: Polypetale

Order: Sapindales

Family: Sapindaceae

Genus: *Sapindus*

Species: *trifoliatus/emarginatus*

**Habitat**

*SE* is a medium sized to large, deciduous tree found in Andhra Pradesh and Karnataka. It is native of south India, grown on the coast and in open forest at low elevations and in the plains of North India. It is commonly found in evergreen
Review of Literature

forests of Konkan and Kanara along with Westren Ghats and South India (Varier, 1997c; Vedavathi et al., 1997b).

**Botanical description of the plant**

SE is a medium sized deciduous tree grown upto a height of 2 m, leaves with pinnate arrangement. Flowers are white, polygamous; fruits are fleshy with black seeds.

**Ethno botanical claims**

The fruit preparations are used to treat ear ache, snake bite, ante-partum and post partum treatment so as to induce and restore the normal condition of uterus after child birth. Roots are used as expectorant, demulcent, (Nadkarni, 1994d; Vedavathi et al., 1997b) and used in hemicranias, hysteria and epilepsy (Varier, 1997c). Leaves are used to treat painful joints, gout and rheumatism (Dastur, 1952b). SE is claimed to be used in hysteria and melancholia.

**Phytochemistry Review**

**Seeds**

Ucciani et al., (1994) reported the presence of cyanolipids from the seed oil of SE. Gupta and Kharya, (1996) evaluated the phytochemical and pharmacolgical studies of the seeds of SE.

**Pericarp**

Yamasaki et al., (2001) isolated and identified acylated triterpene saponins such as heragenin 3-o-2- o-acetyl Beta D- xylopyranosyl)- (1 3) alpha L-rhamnopyranosyl -(1 2) arabinopyranoside, 23 O- acetyl-hederagenin 3- O (4-O-acetyl-beta -D -xylopyranosyl-(1 3), alpha-L-rjhamnopyranosyl -(1 2), alpha -Larabinopyranoside andoleanolic acid 3-o-(4- acetyl-beta -D-xylopyranosyl (1 3)-
alpha rhamnosyl -(1 2) arabinopyranoside and from the pericarp of SE.

Rajesh et al., (2005) reported six saponins from the pericarp of SE and structures were identified by spectral means.

**Pharamacological Review**

**Antifertility effect**

Boghankar et al., (1974) administered alcoholic extract of SE to pregnant albino rats and showed significant antifertility effect.

**Hypotensive effect**

Alcoholic extract of SE at the dose 10-20 mg / kg was administered to male cats and dogs and showed significant hypotensive effect (Singh et al., 1978).

**Antihelmintic effect**

Lal et al., (1978) reported significant antihelminthic effect of SE against Ascardia galli worms in birds by in vitro methods.

**Antispermatogenic and antiandrogenericity effect**

Fruit extract of SE was administered at the dose of 10 mg/kg and showed significant antispermatogenic effect due to testicular lesions and inhibition of spermatogenesis at the primary spermatocyte stage in male gerbils (Dixit and Gupta, 1982).

**Anti fouling effect**

Sawant et al., (1992) reported significant suppression of macrofoulers in estuarine water and bacterial fouler in lab with methanolic extracts of SE on aluminum coupons.
Antinoceptive activity

Arulmozhi et al., (2004a) administered aqueous extract of SE at the dose of 100 mg/kg to rats and showed significant antinociceptive effect against chemical, thermal and nitroglycerin induced hyperalgesia.

Antimigraine activity

Arulmozhi et al., (2004b) administered aqueous extract of pericarp of SE to migraine rabbit and guinea pig models and showed significant antimigraine effect by 5-HT (2B) receptor inhibition and inhibition of serotonin release against induced migraine models.

Anti-inflammatory activity

Arul et al., (2004) administered ethanolic extract of SE to inflammatory models of rats. Inflammation was induced by carageenan and cotton pellet granuloma. SE showed significant inhibition of paw edema, migration of leucocytes and reduction on the granuloma weight induced by cotton pellet.

Arulmozhi et al., (2005d) administered lyophilized aqueous extract of SE at the dose of 20 and 100 mg/kg intraperitoneally to acute inflammatory models of rats and showed significant inhibitory effect against the inflammatory mediators such as 5 COX CTA₂ and NOS.

Antihyperalgesia effect

Arulmozhi et al., (2005a) administered aqueous extract of SE at the dose 2, 20 and 100 mg/kg to migraine models of rats and showed significant antimigraine
and antihyperalgesia effect by studying apomorphine induced climbing behaviour, licking latency on hot plate and the abdominal constrictions.

**Effect on dopaminergic and serotonergic system**

Arulmozhi et al., (2005b) administered aqueous extract of SE at the dose of 20 and 100 mg/kg to migraine models of mice and showed significant inhibition of apomorphine induced climbing behaviour, 1-5HT induced serotonin syndrome and MK-801 induced hyperactivity in mice due to its affinity towards the dopamine D$_2$ and HT$_{2A}$ receptors.

**Effect on central nervous system**

Arulmozhi et al., (2005c) administered aqueous extract of SE at the dose of 100mg/kg to rats and showed significant reduction in thiopental induced sleep, spontaneous locomotor activity and reduced time. SE exhibited no protection against maximal electroshock test and pentylene tetrazole induced convulsions in mice.

**Antibacterial and antifungal effect**

Nair et al., (2005) reported that methanol extract of leaves of SE showed significant antibacterial and antifungal effect against *Pseudomonas, P.morgani, Bacillus subtilius M. flavans and K. pneumonia*.

Rathi et al., (2011) reported that aqueous extract of leaves of SE showed significant antibacterial and antifungal effect against *E.coli, S.epidermis C.glabrata A. flavus and C. albicans*. 
**Antihyperglycemic and anti-diabetic activity**

Jeyabalan and Muralidharan., (2009a) administered ethanolic extract of SE at the dose of 200 and 400 mg/kg to alloxan induced diabetic rats and showed significant antihyperglycemic, antidiabetic and anti-hypertriglyceridemic effect.

**Effect on central nervous system**

Jeyabalan and Muralidharan, (2009b) reported that methanolic extract of pericarp of SE administered at the dose of 50, 100 and 200 mg/kg to rats. SE showed significantly potentiated the sleep induced by phenobarbitone and myorelaxant effect.

**Antihyperlipidemic activity**

Methanol extract of pericarp of SE of various doses were administered to hyperlipidemic rats. SE showed significant decrease in cholesterol and very low density lipoproteins (VLDL) in serum Jeyabalan and Muralidharan, (2009c).

**Antioxidant effect**

Methanolic extract of leaves of SE posesess significant in vitro antioxidant effect proved by DPPH scavenging methods Jeyabalan and Muralidharan, (2010).

**Antiulcer activity**

Kishore et al., (2010) administered methanolic and aqueous extract at the dose of 100, 200 and 400 mg/kg to ulcer models of rats and showed significant antiulcer effect.